

In the Claims:

Please amend claims 1-10, 13-15, and 17-39 as follows:

1. (Amended) [An assay] A method for identifying a compound [with ability to modulate] which modulates interaction or binding between p21 and cyclin D1 and/or cyclin dependent kinase (Cdk) 4, the method including:

- (a) [bringing into contact] contacting p21 or a fragment thereof[, with cyclin D1 and/or Cdk4, or a fragment thereof, and with a test compound, [under conditions] wherein, in the absence of the test compound [being an inhibitor of interaction or binding of p21 and cyclin D1 and/or Cdk 4], the p21 or fragment thereof and the cyclin D1 and/or Cdk4 or fragment thereof interact or bind; and
- (b) determining interaction or binding between the p21 or fragment thereof and the cyclin D1 and/or Cdk 4 or fragment thereof.

2. (Amended)[An assay] A method for identifying a compound [with ability to modulate] which modulates interaction or binding between p21 and cyclin D1 and/or Cdk 4, the method including:

- (a) [bringing into contact] contacting a p21 molecule which comprises an amino acid sequence [substance which includes p21 or a peptide fragment thereof, or a derivative thereof, which is] selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4);

KACRRLFGPVDSEQLSRDCD (peptide 2);

[KxxRRyFzP] KxxRRyFzP (wherein x may be any amino acid, y and z may be hydrophobic, and each of the [underlined] bold residues may be absent or different);

KRRQTSMTDFYHSKRRLIFS;

KRRQTSATDFYH\$KRRLLIFS (peptide 10);

TSMTDFYH\$KRRLLIFS\$KRKP (peptide 11);

KRRLLIFS\$;[, or] and

xyLzF (wherein y and z are any amino acid and x is preferably R),

or a derivative, fragment or [analogue] analog of [a] said fragment, with a substance [including]

comprising cyclin D1 and/or Cdk4, or a derivative or [analogue] analog thereof, and with a test

compound, under conditions wherein, in the absence of the test compound [being an inhibitor of

interaction or binding or said substances,] said [substances] fragment and said substance interact

or bind; and

(b) determining interaction or binding between said [substances] fragment and said substance.

3. (Amended)[An assay] The method according to claim 1 or claim 2 wherein the fragment, derivative or [analogue] analog of p21 [includes] comprises the amino acid sequence of peptide 4.

4. (Amended)[An assay] The method according to claim 1 or claim 2 wherein the fragment, derivative or [analogue] analog of p21 [includes] comprises the amino acid sequence [KxxRRyFzP] KxxRRyFzP.

5. (Amended)[An assay] The method according to claim 4 wherein the fragment, derivative or [analogue] analog of p21 [includes] comprises the amino acid sequence of peptide 2.

6. (Amended)[An assay] The method according to claim 1 or claim 2 wherein the fragment, derivative or [analogue] analog of p21 [includes] comprises the amino acid sequence xyLzF.

7. (Amended)[An assay] The method according to claim 6 wherein the fragment, derivative or [analogue] analog of p21 [includes] comprises the amino acid sequence of peptide

10.

8. (Amended)[An assay] The method according to claim 6 wherein the fragment, derivative or [analogue] analog of p21 [includes] comprises the amino acid sequence KRRLIFSK.

9. (Amended)[An assay] The method according to claim 8 wherein the fragment, derivative or [analogue] analog of p21 [includes] comprises the amino acid sequence of peptide

11.

10. (Amended)[An assay] The method according to any of claims 1 [to 9] or 2 [wherein a compound is additionally tested for ability] further comprising testing the ability of the compound to modulate a p21- mediated effect on Cdk4 activity.

11. (Amended)A method according to claim 10 wherein [the Cdk4 activity includes] RB phosphorylation is tested.

12. (Unamended)A method according to claim 10 wherein induction of G1 cell-cycle arrest is tested.

13. (Amended)A method of identifying a compound [able to modulate] which modulates a p21-mediated effect on Cdk4 activity, the method [including] comprising:
(a) contacting cells with a test compound;

- (b) determining modulation of the p21-mediated effect on Cdk4 activity in the cells;
(c) selecting a compound able to modulate the p21-mediated effect on Cdk4 activity as determined in step (b).

14. (Amended) A method according to claim 13 [wherein ability of a compound able to modulate the p21-mediated effect on Cdk4 activity is also tested] further comprising testing said compound for its ability to interfere with interaction and/or binding between p21 and cyclin D1 and/or Cdk4.

15. (Amended) A method according to claim 13 or claim 14 wherein [the Cdk4 activity includes] RB phosphorylation is tested.

16. (Reiterated) A method according to claim 13 or claim 14 wherein induction of G1 cell-cycle arrest is tested.

17. (Amended) A method [which includes, following identification of] comprising identifying a compound [as being able to interfere] which interferes with interaction or binding between p21 and cyclin D1 and/or Cdk4 and/or [modulate] modulates a p21-mediated effect on Cdk4 activity in accordance with any of claims 1 [to 16] or 2, further comprising formulating [formulation of] the compound into a composition including at least one additional component.

18. (Amended) [Use of a substance which includes] A p21 [or a] peptide fragment [thereof, or a derivative thereof,] consisting essentially of an amino acid sequence selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4);

KACRRLFGPVDSEQLSRDCD (peptide 2);

300
[KxxRRyFzP] **KxxRRyFzP** (wherein x may be any amino acid, y and z may be hydrophobic, and each of the [underlined] bold residues may be absent or different);
KRRQTSMTDFYHSKRRLIFS;
KRRQTSATDFYHSKRRLIFS (peptide 10);
TSMTDFYHSKRRLIFSKRKP (peptide 11);
KRRLIFSK;[, or] and
xyLzF (wherein y and z are any amino acid and x is preferably R),
or a derivative, fragment or [analogue] analog of a said fragment, which is capable of interacting
[able to interact] with or [bind] binding to cyclin D1 and/or Cdk4[, in screening for compounds
able to modulate interaction or binding between p21 and cyclin D1 and/or Cdk4].

19. (Amended)[Use of a substance which includes] A p21 [or a] peptide fragment
[thereof, or a derivative thereof,] consisting of an amino acid sequence selected from the group
consisting of:
RERWNFDFVTETPLEGDFAW (peptide 4);
KACRRLFGPVDSEQLSRDCD (peptide 2);
[KxxRRyFzP] **KxxRRyFzP** (wherein x may be any amino acid, y and z may be hydrophobic,
and each of the [underlined] bold residues may be absent or different);
KRRQTSMTDFYHSKRRLIFS (peptide 10);
KRRQTSATDFYHSKRRLIFS (peptide 11);
TSMTDFYHSKRRLIFSKRKP;
KRRLIFSK;[, or] and
xyLzF (wherein y and z are any amino acid and x is preferably R),
[r a derivative, fragment or [analogue] analog of a said fragment, which is capable of interacting
[able to interact] with or [bind] binding to cyclin D1 and/or Cdk4[, in screening for compounds
able to modulate a p21-mediated effect on Cdk4 activity].

20. (Amended)[Use according to] A method of modulating [claim 19 wherein the Cdk4 activity includes] RB phosphorylation comprising contacting a cell with a peptide of claim 18.

21. (Amended)[Use according to] A method of [claim 18 wherein induction of] modulating G1 cell-cycle arrest [is tested] comprising contacting a cell with a peptide of claim 18.

22. (Amended)[Use according to any] The method of any of claims [18 to 21] 13 or 14 wherein the fragment, derivative or [analogue] analog of p21 includes the amino acid sequence of peptide 4.

23. (Amended)[Use according to] The method of any of claims [18 to 21] 13 or 14 wherein the fragment, derivative or [analogue] analog of p21 includes the amino acid sequence KxxRRyFzP.

24. (Amended)[Use according to] The method of claim 23 wherein the fragment, derivative or [analogue] analog of p21 includes the amino acid sequence of peptide 2.

25. (Amended)[Use according to] The method of any of claims [18 to 21] 13 or 14 wherein the fragment, derivative or [analogue] analog of p21 includes the amino acid sequence xyLzF.

26. (Amended)[Use according to] The method of claim 25 wherein the fragment, derivative or [analogue] analog of p21 includes the amino acid sequence of peptide 10.

27.(Amended)[Use according to] The method of claim 25 wherein the fragment, derivative or [analogue] analog of p21 includes the amino acid sequence KRRLIFSK.

28. (Amended)[Use according to] The method of claim 27 wherein the fragment, derivative or [analogue] analog of p21 includes the amino acid sequence of peptide 11.

29. (Amended)A method of [designing] identifying mimetics of p21 [having the biological activity of Cdk4 binding or inhibition, the activity of allosteric inhibition of Cdk4 and/or the activity of cyclin D1 binding, said method] comprising:

(i) [analysing] defining a pharmacophore by modifying the amino acid sequence of a peptide [a substance] having [the] a biological activity selected from the group consisting of: the ability to bind to or inhibit Cdk4, the ability to allosterically inhibit Cdk4, and the ability to bind to cyclin D1 to determine [the] which amino acid residues are essential and important for [the] said activity [to define a pharmacophore]; and

(ii) [modelling] modeling the pharmacophore to [design and/or screen candidate] identify mimetics having the biological activity.

30. (Amended)[A] The method of [which includes, following identification of a mimetic as having the biological activity of Cdk4 binding or inhibition, the activity of allosteric inhibition of Cdk4 and/or the activity of cyclin D1 binding in accordance with] claim 29, further comprising [formulation of] formulating the mimetic into a composition including at least one additional component.

31. (Amended)[Use of a substance] A method of treating a hyperproliferative disorder in a cell which comprises contacting the cell with a substance selected from the group consisting of:

(i) a fragment of p21, or an active portion or derivative thereof;

(ii) a peptide fragment including the motif xyLzF, wherein y and z are any amino acid and x derivative of said peptide fragment inhibiting Cdk4;

(iii) a peptide fragment including the motif [KxxRRyFzP] **KxxRRyFzP**, wherein x is any amino acid, y and z may be hydrophobic, and each of the [underlined] bold residues may be absent or different; [or] and

([iii]iv) a functional mimetic of (i), (ii) or (iii) with the property of inhibiting Cdk4; [in the manufacture of a medicament for inhibiting Cdk4, for the treatment of a disorder mediated by Cdk4 activity, or for the treatment of] such that a hyperproliferative disorder [by inhibiting Cdk4] is treated.

32. (Amended)[Use according to claim] The method of claim 31 wherein the substance comprises or consists essentially of a peptide fragment with a sequence which is selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4);

KACRRLFGPVDSEQLSRDCD (peptide 2);

KRRQTSMTDFYHSKRRLIFS;

KRRQTSATDFYHSKRRLIFS (peptide 10);

TSMTDFYHSKRRLIFSKRKP (peptide 11);

[or] and KRRLIFSK,

or a functional mimetic of any of these peptide sequences with the property of inhibiting Cdk4.

33.(Amended) [Use according to] The method of claim 32 wherein the substance consists essentially of the peptide KRRLIFSK or a functional mimetic thereof [with the property of inhibiting] which inhibits Cdk4.

34. (Amended)[Use according to] The method of any of claims 31 to 33 wherein the substance is coupled to a carrier for delivery to cells.

35. (Amended)[Use according to] The method of claim 34 wherein the substance is a peptide and is coupled to a carrier peptide with the sequence RQIKIWFQNRRMKWKK.

36. (Amended)A method of ameliorating a disorder characterized by abnormal cell proliferation comprising contacting a cell with[The] the peptide KRRLIFSK, or a functional mimetic thereof with the property of inhibiting Cdk4[, for use in a method of treatment of the human or animal body by therapy] such that abnormal cell proliferation is ameliorated.

37. (Amended)The method according to claim 36, wherein the [The peptide or functional mimetic thereof according to claim 36 wherein the treatment is of] disorder is a hyperproliferative disorder.

38. (Amended)A method of interfering with interaction between p21 and cyclin D1 and/or Cdk4, [the method including] comprising contacting p21 and/or Cdk4 with a substance which includes a peptide fragment of p21 or a derivative thereof which is selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4);

KACRRLFGPVDSEQLSRDCD (peptide 2);

[KxxRRyFzP] KxxRRyFzP (wherein x may be any amino acid, y and z may be hydrophobic, and each of the [underlined] **bold** residues may be absent or different);

KRRQTSMTDFYHSKRRLIFS;

KRRQTSATDFYHSKRRLIFS (peptide 10);

TSMTDFYHSKRRLIFSKRKP (peptide 11);

KRRLIFSK₁; [or] and

xyLzF (wherein y and z are any amino acid and x is preferably R)₁; or a derivative, fragment, [analogue] analog or functional mimetic of [a] said fragment.

39. (Amended) A method of modulating a p21-mediated effect on Cdk4 activity, the method including contacting p21 and/or Cdk4 with a substance which [includes] comprises a peptide fragment of p21, or a derivative thereof, which is selected from the group consisting of:

RERWNFDFVTETPLEGDFAW (peptide 4);

KACRRLFGPVDSEQLSRDCD (peptide 2);

[KxxRRyFzP] KxxRRyFzP (wherein x may be any amino acid, y and z may be hydrophobic, and each of the [underlined] bold residues may be absent or different);

KRRQTSMTDFYHSKRRLIFS₁

KRRQTSATDFYHSKRRLIFS (peptide 10);

TSMTDFYHSKRRLIFSKRKP (peptide 11);

KRRLIFSK₁; [or] and

xyLzF (wherein y and z are any amino acid and x is preferably R)₁

or a derivative, fragment, [analogue] analog or functional mimetic of a said fragment.

40. (Unamended) A method according to claim 38 or claim 39 which takes place in vitro or ex vivo.

41. (Unamended) A method according to claim 39 which takes place in vivo.